

Remarks

This is in response to the Official Action mailed November 15, 2007 (Paper No./Mail Date 20071024). Applicants note with appreciation the Examiner's courtesy and professionalism during the Office interview conducted (via telephone) on January 10, 2008.

Claims 1, 2, and 4-12 are pending.

Claim 1 has been amended to specifically recite that the first step in the method represents transferring a solid phase resin suspension (e.g., Paragraph 0011 of the specification as filed) from a resin source external to the microwave transparent vessel into the microwave transparent vessel.

As discussed during the interview and as set forth in these written remarks, this (among other factors) distinguishes the claimed invention from those references in which amino acids are attached to an external surface of a solid support such as a cellulosic membrane or silica gel on a slide.

The Applicants have made a number of comments about the invention in the various responses filed previously and the Applicants' remarks herein are consistent with those comments. During the interview, the Applicants emphasized the point that during peptide synthesis, the deprotection step offers the risk of undesired racemization. Accordingly, in conventional thinking, microwave irradiation (or other aggressive steps) should be avoided in order to help avoid such undesired racemization.

In contrast to such conventional thinking, the claimed invention carries out a plurality of deprotection steps while applying microwave energy to the reagents.

The Office Action offers five grounds of rejection. These will be addressed in turn under their respective headings.

The § 102 Rejection of Claims 1-4 Based on
Martin 20030082633 using Hilpert

First, the Office Action continues to reject Claim 1 as anticipated by Examples 12 and 13 of the Martin publication.

Anticipation requires that a single prior art reference expressly or inherently discloses each and every limitation of the claimed invention, *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F2d 1565 (Fed. Cir. 1991). Applicant must continue to respectfully traverse any anticipation argument based upon Martin on the grounds that Martin fails to contain all of the elements recited in Claim 1 within its four corners.

Martin and its incorporated references fails to include all of the elements of the claimed invention within the four corners of Martin or within the four corners of the references incorporated by Martin.

The Examiner admits that at a minimum, the Hilpert reference must be included as a part of Martin's Examples 12 and 13:

"Claims 1 and 4 are rejected under 35 U.S.C. 102(a) or under 102(e) as being anticipated by Martin et al. (US 2003/0082633) as evidenced by Hilpert et al. (Protein Engineering, 2001)."

(Page 3 of the November 15, 2007 Office Action).

A reference, however, must be considered in full. Thus, the explicit language of Martin's Example 12 reads as follows:

"Synthesis procedure is as described (Hilpert et al., 2001 and references cited therein, and Sigma-Genosys technical notes) with the exception that reaction times are shorted (sic) where appropriate by a factor of 2 to 20-fold and the shortened reactions are carried out under irradiation by microwaves into microwave oven."

Therefore, if Martin contains all of the elements of Claim 1 within its four corners, it can only do so based upon the incorporation of (1) Hilpert and (2) the “references cited” in Hilpert and (3) the “Sigma-Genosys technical notes.”

Stated differently, Martin explicitly states that both Hilpert and the Sigma-Genosys notes are required in order to practice Example 12.

Nevertheless, Martin fails to formally reference the Sigma-Genosys technical notes, and the Examiner has likewise failed to formally reference or produce them—even though they were first cited by the Examiner in the December 15, 2006 Office Action. Neither of the following two Office Actions (March 23, 2007 and November 15, 2007) have produced the Sigma-Genosys notes.

Instead, following Applicants’ previous request for the Sigma-Genosys notes, the Examiner has only been able to produce an unrelated set of “Frequently Asked Questions” from the Sigma-Genosys website.

The Examiner has taken the position “that Sigma-Genosys was not cited in the rejection and that Sigma- Genosys is a company that one skilled in the art would have been able to refer to at the time the invention was made by Martin.” (Page 7 of the November 15, 2007 Office Action).

This is a self-contradicting argument. If Martin anticipates because of the explicit contents of Hilpert and Sigma-Genosys, then Hilpert and Sigma-Genosys are part of the rejection.

Instead, having cited Martin’s Example 12 as anticipating on Page 3, the Examiner is attempting to argue on Page 7 that Martin’s incorporated references need be neither produced nor considered. “It is too much like the road which was so crooked that the traveler who entered upon it had only proceeded a few steps when he met himself coming back.” Lyon, Elements of Debating (1919).

Applicant respectfully submits that Martin cannot be made a part of any § 102 rejection unless and until the Sigma-Genosys technical notes can be identified and produced.

Logically, however, the Sigma-Genosys notes can never be produced because Martin failed to identify them in the patent application in the first place. Thus, even if a reference entitled "Sigma-Genosys technical notes" could eventually be identified, no logical basis would exist to confirm that they were the notes referred to by Martin.

Stated formally, the lack of the Sigma-Genosys technical notes renders Martin non-enabling for the purposes asserted by the Examiner. In order to anticipate the claimed invention, Martin must enable the claimed invention. If Martin fails to enable the claimed invention, its enablement of other techniques remains irrelevant to the anticipation issue.

Adding peptide precursors to paper or chromatography media fails to anticipate placing a solid phase resin suspension into a microwave transparent vessel.

As an entirely separate grounds for removing the § 102 rejection, Claim 1 now recites that a solid phase resin suspension is transferred into a reaction vessel. This clearly distinguishes over any techniques in which peptides are placed onto external surfaces such as Martin's cellulosic membranes.

Words are the only tools available to the inventor. "Things are not made for the sake of words, but words for things." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 US 722 (2002), citing *Autogiro Co. of America v. United States*, 384 F.2d 391 (Ct. Cl. 1967).

Accordingly, when the inventors describe and claim the step of placing a solid phase peptide resin suspension into a vessel, this must logically be distinguished from adding drops of peptide precursors to a cellulosic membrane or to a surface coated with a chromatography media (e.g., the Williams '434 patent).

Additionally, when the inventors describe and claim the use of a microwave transparent vessel, this must be logically distinguished from microwave-absorbing structures such as Martin's glass-titanate-glass sandwich which Martin specifically describes, creates, and uses for the purpose of absorbing (rather than transmitting) microwaves (e.g., Martin's Abstract and Claim 1).

Obviousness

Given that four different obviousness combinations have been applied against the claims, Applicants believe that a review of obviousness is appropriate.

In the present U.S. legal landscape, the obviousness evaluation is framed in terms of one long-standing case and one recent case; i.e., *Graham v. John Deere* 383 U.S. 1 (1966) and *KSR v. Teleflex*, 127 S. Ct. 1727; 167 L. Ed. 2d 705 (2007).

Graham's discussion is long-standing and often-repeated:

"Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy." *Graham v. John Deere Co.*, 383 U.S. 1 at 17-18,

KSR affirms *Graham*:

"In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966), the Court set out a framework for applying the statutory language of § 103 While the sequence of these questions might be reordered in any particular case, the factors continue to define the inquiry that controls."

127 S.Ct. at 1734, 15 L.Ed. 2d at 715.

Thus, instead of challenging or moderating the *Graham* analysis or the secondary considerations, *KSR* instructs inventors, the Patent Office, and litigators to avoid a "rigid" (127 S.Ct. at 1741, 15 L.Ed. 2d at 722) application of the TSM (teaching, suggestion, motivation) test that had been widely used by the Court of Appeals for the Federal Circuit. The goal in *KSR* is to reasonably avoid a "patent for a combination which only unites old elements with no change in their respective functions" (because such a patent) . . . "obviously withdraws what is already known into the field of its monopoly and diminishes the resources

available to skillful men.”(*KSR*, 127 S.Ct. at 1739, 15 L.Ed. 2d at 720 citing *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, (1950)).

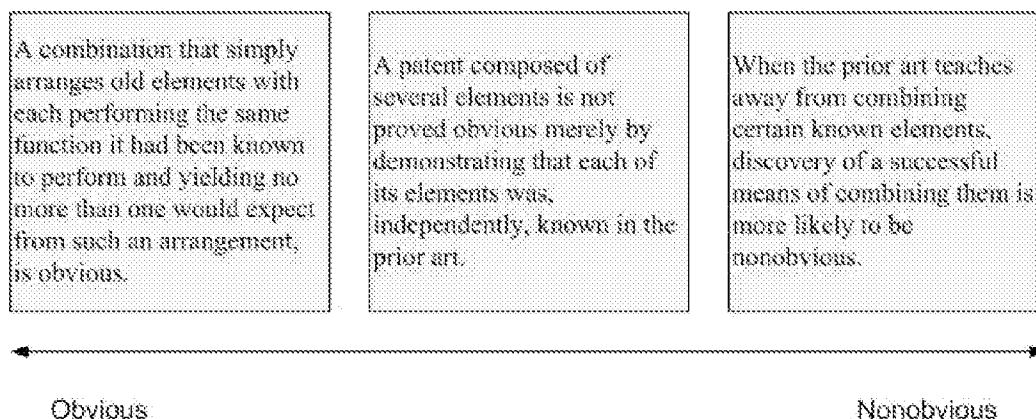
KSR also maintains the long-standing doctrine that teaching away from a reference is an indication of non-obviousness,

The Court relied upon the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. *Id.*, at 51-52, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293.

127 S.Ct. at 1740, 15 L.Ed. 2d at 721. *KSR* balanced this with the following, *Id.*:

Finally, in *Sakraida V. Ag Pro, Inc.*, 425 U.S. 273, 96 S. Ct. 1532, 47 L. Ed. 2d 784 (1976), the Court derived from the precedents the conclusion that when a patent "simply arranges old elements with each performing the same function it had been known to perform" and yields no more than one would expect from such an arrangement, the combination is obvious. *Id.*, at 282, 96 S. Ct. 1532, 47 L. Ed. 2d 784.

Taking these quotes from *KSR* as guidance, a diagram (admittedly simplified) of the obvious-to-nonobvious spectrum might appear as follows:



The § 103(a) Rejection of Claims 1,4 and 6-8 Based on Yu,
Williams 6858434 and Martin 20030082633

First, Applicants submit that the problems that render Martin inappropriate as a § 102 reference likewise make it inappropriate as a § 103 reference; i.e., because the skilled person lacks access to the Sigma Genosys notes, Martin fails to provide the enablement required to qualify as an appropriate reference as against these pending claims.

Yu presents its own enablement problems. Yu goes no further than two simple coupling scenarios: (i) coupling two single amino acids to produce a two-acid peptide or (ii) coupling two prepared peptide fragments to produce a longer peptide. Accordingly, Yu fails to enable any peptide synthesis that requires more than a single coupling reaction.

Even putting those problems aside, however, the combination of Yu and Williams is logically inappropriate. In particular, Yu discloses a resin-based solid phase peptide synthesis in which a single coupling step is carried out in a conventional microwave oven. Williams, however, is a combinatorial library screening technique in which a Boc-protected amino acid (the Examiner cites Example 5 at column 12 beginning at line 15) is deposited on silica gel on a thin chromatography plate and then deprotected in a conventional microwave oven.

More importantly, Williams teaches away from the resin suspensions recited in the pending claims (e.g., Column 1 lines 33-65), and no reason exists other than the road map provided by the pending claims to attempt to combine the protection in a thin layer chromatography context with coupling in a resin-based suspension context.

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The § 103(a) Rejection of Claims 1, 2, 5, and 9-12 Based on Yu,
Stadler, Santagada and Martin 20030082633

The arguments just presented with respect to the Martin and Yu references are incorporated herein by reference.

That said, Stadler and Santagada add nothing that cures the Martin and Yu deficiencies.

The Santagada reference has been applied for the use of specific activators in a single microwave enhanced coupling reaction. Accordingly, regardless of the combination in which it is used, Santagada offers no cure for the weaknesses in the base references or the combinations.

As admitted by the Examiner (page 12 of the March 23, 2007 Office Action) Stadler offers nothing beyond attaching or cleaving carboxylic acids to and from resins. Accordingly, it cannot support or cure or the failures of Martin or the other base references or produce a useful combination with them.

The § 103(a) Rejection of Claims 1 and 6-8 Based on Yu,
Williams 6858434 and Cargill 6171555

The arguments just presented with respect to the inappropriate combination of Yu and Williams remain, of course, entirely appropriate. Yu offers nothing other than simple coupling scenarios. Williams teaches away from solution techniques and instead offers nothing other than deprotection of a library of single amino acids on silica gel on chromatography plates.

Cargill adds nothing to the combination that suggests the claimed invention to the skilled person. Cargill discloses a reaction block docking station suitable for use in combinatorial chemistry techniques. Cargill makes background reference to solid phase synthesis of peptides, and mentions—in connection with the instrument but never with

specific methods or reactions—that the described reaction block could be used in a microwave instrument if it were formed of nonmetallic materials.

Interestingly enough, however, Cargill supports the Applicants' position that the skilled person is well aware of the difference between microwave-transparent and microwave-absorbing materials.

The § 103(a) Rejection of Claims 1, 2, 5, and 9-12 Based on Yu,
Williams 6858434, Cargill 6171555, Stadler and Santagada

As noted earlier, nothing about Stadler and Santagada cure the individual weaknesses of Yu, Williams or Cargill, nor do they mend the flaws inherent in the Yu-Williams, or Yu-Williams-Cargill combinations.

In particular, the silica gel techniques of Williams are inconsistent with the reaction block instrument of Cargill. Thus, the skilled person would have no reason to combine them other than in a hindsight attempt to reach the recitations of the pending claims. As repeated several times, Yu and Santagada offer nothing other than single simple couplings while Stadler shows simple coupling of unrelated compounds.

Applicants accordingly submit that this version of the combination must be removed as against the pending claims.

Applicants accordingly submit that the pending claims are in condition for immediate allowance, and the same is respectfully requested.

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Respectfully submitted,

A handwritten signature in black ink, appearing to read "Philip Summa", followed by a long horizontal line.

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